REMARKS

Claims 54 and 57 are pending in this application. Claim 54 has been amended. No claims have been cancelled. No new claims have been added.

Claim 54 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner notes that there is no antecedent basis for the R^{I} and R^{II} substituents in R_9 of the compounds of Formula II. These substituents should have properly been designated as R' and R" since they further define the R_9 substituents recited in claim 54 that include R' and R", namely, C(O)OR', –alkyl-aryl–C(O)OR', –alkyl–OC(O)R', –alkyl–C(O)R', –alkyl–C(O)OR', –alkyl–N(R")C(O)R', and –alkyl–N(R")C(O)OR'. As to the phrase "as applicable" recited in the definition of the R_8 substituents of Formula I, this phrase has been deleted. In view of these amendments, applicants believe that the rejection of claim 54 under the second paragraph of § 112 has been traversed.

Claims 54 and 57 have also been rejected under 35 U.S.C. § 112, first paragraph, it being the Examiner's position that the specification does not reasonably provide enablement for R' and R" of formula I coming together to form all of the heterocyclic rings claimed, R_1 and R_2 of formulas I and II coming together to form an oxadiazole, and the R' and R'' substituents of R_9 of the compounds of formula II coming together to form heterocycle, the heterocycle being optionally substituted with halogen, cyano, NO_2 or lactone. Applicants submit that this rejection is not well-founded and should be withdrawn as detailed below.

With respect to the Examiner's first objection, the specification cites US Patent No. 4,777,167 which describes R' and R" coming together to form piperidino and pyrrolidino. Other prior art shows, for example, morpholino (Sincar, I. et al., *Journal of Medicinal Chemistry*, 1991, 34, 2248-60); thiomorpholino (US Patent No. 4,618,607); and piperazino (US Patent No. 5,034,395). In view of the specific teachings of the present specification and the general level of skill in the art as exemplified by the above-cited references, a skilled person would readily know how to make compounds wherein R' and R" of formula I come together to form the heterocyclic rings recited in the claims.

As to the Examiner's second objection, the oxadiazole compounds can be easily prepared by using the appropriate aldehyde (aldehyde 1f of scheme II) and following

reaction scheme II. The use of this aldehyde for making dihydropyridines and the preparation of this oxadiazole-fused benzaldehyde is well documented in the art. See, for example, Leonardi, A., et al., *European Journal of Medicinal Chemistry*, 1998, 33, 399-420; Gasco, A. M., et al., *European Journal of Medicinal Chemistry*, 1996, 31, 3-10; CH 661270. Aldehyde If is also commercially available from MicroChemistry Building Blocks, Order No. mch-bb 2391.

With regard to the Examiner's third objection, the claims do not state that the R' and R" substituents on R_9 of the compounds of Formula II come together to form a ring, as suggested by the Examiner. Accordingly, applicants do not understand the basis of this rejection and request that it be withdrawn.

Claims 54 and 57 have also been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants maintain that this rejection is not well-founded as discussed below.

The disclosure fully enables those skilled in the art to practice the claimed methods. The use of dihydropyridine-type calcium channel blockers in treating disorders such as hypersensitivity, allergy, asthma and bronchospasm is well-known in the art, as established by the art already of record in this application. It is further noted that because the compounds administered according to the claimed method of treatment are short acting they exert their effects locally. Thus, these compounds, when administered locally to the lungs, are particularly effective for treating the enumerated disorders. The specification at, for example, page 13, lines 12-24, discloses a number of formulations for local administration of these compounds to the lungs via inhalation, including a solution intended for administration by metered dose inhale, or in a form suitable for a dry powder inhaler or insufflator. Typically, administration via inhalation is accomplished by delivering the specified compounds in the form of an aerosol spray from a pressurized container using a suitable propellant and a valve to deliver a metered dose, as is pointed out in the specification and as is well-known in the art.

In view of the scope of the disclosure and the level of skill in the art with respect to the use of dihydropyridine-type calcium channel blockers, applicants submit that method of treatment claims 54 and 57 are fully enabled. Accordingly, applicants request that the rejection of claims 54 and 57 under 35 U.S.C. § 112, first paragraph, be withdrawn and that a Notice of Allowance with respect to these claims be issued at the earliest possible date.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version With Markings To Show Changes Made".

Applicants hereby petition for a one-month extension of time to respond to the Office Action dated August 19, 2002. Please charge the fee required under 37 C.F.R. 1.17(a), any deficiencies in this fee or any other fees that may be required to Deposit Account No. 10-0750/ORT-1477/JSK.

Applicants are also filing herewith a Request for Continued Examination pursuant to 37 C.F.R. § 1.114. In addition, applications are filing herewith an Information Disclosure Statement under 37 C.F.R. § 1.97(c). Applicants do not believe that any fees are required in connection with the filing of this Information Disclosure Statement; however, should any fees be necessary please charge Deposit Account No. 10-0750/ORT-1477/JSK.

Should the Examiner have any questions regarding this Response, please contact the undersigned attorney at the telephone number listed.

Respectfully submitted,

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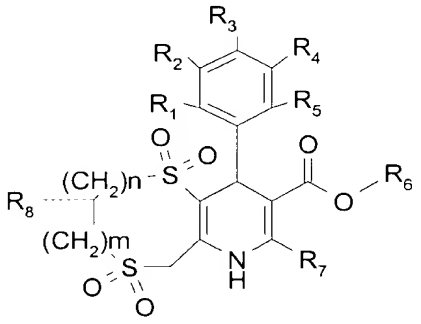
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 54 as follows:

54. (twice amended) A method of treating a subject suffering from a disorder selected from the group consisting of hypersensitivity, allergy, asthma and bronchospasm, which method comprises administering to the subject a therapeutically effective dose of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula I or Formula II,

wherein Formula I is as follows:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

(a) R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, OH, halogen, cyano, NO_2, alkyl, C_{1-8} alkoxy, C_{1-8} alkylsulfonyl, C_{1-4} carboalkoxy, C_{1-8} alkylthio, difluoromethoxy, difluoromethylthio, trifluoromethyl, and oxadiazole (formed by R_1 and R_2);

(b) R_6 is selected from the group consisting of H, C_{1-5} straight or branched alkyl, aryl, 3-piperidyl, N-substituted 3-piperidyl, N-substituted 2-pyrrolidinyl methylene, and substituted alkyl, wherein

said N-substituted 3-piperidyl and said N-substituted 2-pyrrolidinyl methylene may be substituted with C_{1-8} straight or branched chain alkyl or benzyl, and said substituted alkyl may be substituted with C_{1-8} alkoxy, C_{2-8} alkanoyloxy, phenylacetyloxy, benzoyloxy, hydroxy, halogen, p-tosyloxy, mesyloxy, amino, carboalkoxy or NR'R", wherein

(i) R' and R" are independently selected from the group consisting of H, C_{1-8} straight or branched alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and phenethyl, or (ii) R' and R" together form a heterocyclic ring selected from the group consisting of piperidino, pyrrolidino, morpholino, thiomorpholino, piperazino, 2-thieno, 3-thieno, and an N-substituted derivative of said heterocyclic rings, said N-substituted derivative being substituted with H, C_{1-8} straight or branched alkyl, benzyl, benzhydryl, phenyl and/or substituted phenyl (substituted with NO_2, halogen, C_{1-8} straight or branched chain alkyl, C_{1-8} alkoxy and/or trifluoromethyl);

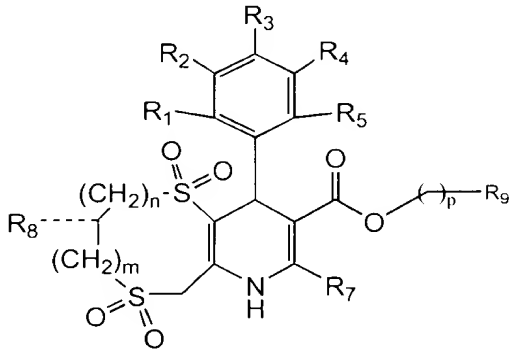
(c) R_7 is selected from the group consisting of H, amino, alkyl, aryl, trifluoromethyl, alkoxymethyl, 2-thieno and 3-thieno;

(d) R_8 is connected to the bis-sulfone ring via a single or double bond[, as applicable,] and is selected from the group consisting of H, alkylhydroxy, alkenyl, amino, phenyl, benzyl, C_{1-8} straight or branched alkyl, trifluoromethyl, alkoxymethyl, C_{3-7} cycloalkyl, substituted benzyl, formyl, acetyl, t-butyloxy carbonyl, propionyl, substituted alkyl and R'"CH_2C=O, wherein (i) said substituted benzyl is substituted with halogen, trifluoromethyl, C_{1-8} straight and/or branched alkyl or C_{1-8} alkoxy, (ii) said substituted alkyl is substituted with amino, dialkyl

amino, C_{1-8} alkoxy, hydroxy and/or halogen, and (iii) R''' is amino, dialkyl amino, C_{1-8} alkoxy, hydroxy or halogen; and

(f) m, n, and their sum are each an integer from 0 to 4;

and wherein Formula II is as follows:



Formula II

or a pharmaceutically acceptable salt thereof, wherein

(a) R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, OH, halogen, cyano, NO_2, alkyl, C_{1-8} alkoxy, C_{1-8} alkylsulfonyl, C_{1-4} carboalkoxy, C_{1-8} alkylthio, difluoromethoxy, difluoromethylthio, trifluoromethyl, and oxadiazole (formed by R_1 and R_2);

(b) R_7 is selected from the group consisting of H, amino, alkyl, aryl, trifluoromethyl, alkoxymethyl, 2-thieno and 3-thieno;

(c) R_8 is connected to the bis-sulfone ring via a single or double bond and is selected from the group consisting of H, alkylhydroxy, alkenyl, amino, phenyl, benzyl, C_{1-8} straight or branched alkyl, trifluoromethyl, alkoxymethyl, C_{3-7} cycloalkyl, substituted benzyl, formyl, acetyl, t-butyloxy carbonyl, propionyl, substituted alkyl and R'''CH_2C=O,

wherein (i) said substituted benzyl is substituted with halogen, trifluoromethyl, C_{1-8} straight and/or branched alkyl or C_{1-8} alkoxy, (ii) said substituted alkyl is substituted with amino, dialkyl amino, C_{1-8} alkoxy, hydroxy and/or halogen, and (iii) R''' is amino, dialkyl amino, C_{1-8} alkoxy, hydroxy or halogen;

(d) R_9 is selected from -alkyl-OH, alkylamine, lactone, cyclic carbonate, alkyl-substituted cyclic carbonate, aryl-substituted cyclic carbonate, –aryl–C(O)OR', –alkyl-aryl–C(O)OR', –alkyl–OC(O)R', –alkyl–C(O)R', –alkyl–C(O)OR', –alkyl–N(R")C(O)R', and –alkyl–N(R")C(O)OR', wherein

[R^I and R^{II}] R' and R" are independently selected from the group consisting of hydrogen, amino, alkyl, aryl, aryl-fused cycloalkyl, and heterocyclyl, the amino, alkyl, aryl, aryl-fused cycloalkyl, and heterocyclyl being optionally substituted with halogen, cyano, NO_2, lactone, amino, alkylamino, aryl-substituted alkylamino, amide, carbamate, carbamoyl, cyclic carbonate, alkyl, halogen-substituted alkyl, arylalkyl, alkoxy, heterocyclyl and/or aryl (the aryl being optionally substituted with OH, halogen, cyano, NO_2, alkyl, amino, dimethylamino, alkoxy, alkylsulfonyl, C_{1-4} carboalkoxy, alkylthio and/or trifluoromethyl);

(e) m, n, and their sum are each an integer from 0 to 4; and

(f) p is an integer from 0 to 4.